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Dental Abnormalities in Children Treated for Neuroblastoma

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Purpose. To determine the frequency and types of dental abnormalities among children treated at a young age for cancer, as represented by neuroblastoma.

Patients and Methods. We retrospectively reviewed the dental records and panoramic radiographs of 542 children who were treated for neuroblastoma at our institution over a 31-year period. Patients in our study had to meet the following criteria: they were treated on an institutional protocol, they had undergone panoramic radiography, and their dental follow-up continued for at least 2 years after diagnosis. We evaluated the frequency of clinically or radiographically apparent microdontia, excessive caries, root stunting, hypodontia, and enamel hypoplasia in our study population.

Results. Of the 52 patients who met the study criteria, 71% developed dental abnormalities, comprising microdontia in 38%, excessive caries in 29%, root stunting in 17%, hypodontia in 17%, and enamel hypoplasia in 17%. In nearly half (23) of our patients, neuroblastoma was diagnosed on or before their first birthday.

Conclusion. Children treated for neuroblastoma are at high risk for abnormal dental development. The abnormalities in these patients may require extensive dental care and can compromise their quality of life. Frequent dental examinations and an intense oral hygiene program before, during, and after treatment may improve overall dental health. Med. Pediatr. Oncol. 30:22–27, 1998.

Key words: late effects; neuroblastoma; dental sequelae; microdontia; hypodontia; root stunting

INTRODUCTION

Aggressive treatment regimens may have a dramatic impact on the health and quality of life of long-term survivors of cancer [1–10]. In addition, late adverse effects of therapy are becoming increasingly prevalent due to improved survival rates among infants and children; these treatment-associated sequelae include dental abnormalities. Chemotherapy [3,6,11–13] and radiation therapy [1–3,13–16] have been implicated in various dental abnormalities, the type and severity of which reflect the timing of the insult during dental development [3,8,14]. The types and frequencies of dental sequelae in children treated at a young age for cancer have not been described extensively. Therefore the study of dental abnormalities in children treated at a young age for neuroblastoma may provide insight into altered odontogenesis from oncotherapy.

Approximately 525 cases of neuroblastoma are diagnosed each year in the United States. Accounting for 8 to 10 percent of all childhood cancers, this neoplasm is the most common extracranial childhood solid tumor [17]. The early age at which children are treated for neuroblastoma (median age at diagnosis, 22 months [18]) places their primary and permanent teeth at risk for altered development. The primary dentition begins to develop at about 6 weeks of gestation and continues until about the age of 3 years, at which time the tooth roots have completed growth [19]. Further, development of some permanent teeth is very active between the ages of 4 and 6 years [20,21], peak times of diagnosis and treatment of neuroblastoma [18]. To assess the incidence and distribution of dental abnormalities among children with neuroblastoma, we retrospectively reviewed the dental records and panoramic radiographs of 52 patients. These children received multiagent chemotherapy and were followed for at least 2 years after diagnosis of the malignancy.

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PATIENTS AND METHODS

From July 1963 through July 1994, 542 children were treated for neuroblastoma at St. Jude Children's Research Hospital; these patients were staged according to the St. Jude [22] and Pediatric Oncology Group (POG) [23] staging systems. We retrospectively reviewed the medical and dental records of these children. Patients eligible for inclusion in our study population had to meet the following criteria: they were treated on an institutional protocol, they had undergone panoramic tomography, and their dental and radiographic follow-up continued for at least 2 years after diagnosis.

Due to the technical requirements of the examination, panoramic radiographs typically were not obtained until the patient was at least 3 years old. The children in the study population received thorough dental examinations whenever panoramic tomograms were obtained. A pediatric dentist (KPH) and a pediatric radiologist (SCK) evaluated all panoramic radiographs.

We recorded the clinically or radiographically apparent dental abnormalities in our patients. These abnormalities comprised hypodontia (absent teeth), microdontia (abnormally small teeth), enamel hypoplasia (abnormally irregular enamel), root stunting (shortened root length), and excessive caries. Characterized according to the dft (decayed, filled teeth) classification system [24], clinical caries was considered to be excessive if a patient had more than four dft.

Because our 52 patients were each treated according to one of nine therapeutic protocols, we did not attempt to determine the risk of dental abnormalities associated with each regimen. Instead, we compared the frequency and types of dental abnormalities of patients who were diagnosed with neuroblastoma when they were $\leqslant$1 year of age to those of children who presented when they were older than 1 year. The majority of younger children received cyclophosphamide and doxorubicin; the older patients were treated with multiagent chemotherapy including cyclophosphamide, doxorubicin, cisplatin, and etoposide.

RESULTS

Patients and Treatment

Of the 452 patients treated for neuroblastoma at our institution during the 31-year study period, 52 met the inclusion criteria (Table I). Of these 52 patients, 19 were girls; 36 of the children were white, 9 were black, and 7 were Hispanic. The median age of the study patients at diagnosis was 1.5 years (range, 3 days to 7.2 years; mean, 1.9 years). Only 8 of these children received head and/or neck irradiation, either as part of a preparative regimen for bone marrow transplantation (n = 2) or as local therapy of a metastasis (n = 6). The study patients were followed radiographically for a median of 5.0 years (range, 1.9 to 19.3 years; mean, 6.4 years).

TABLE I. Percentage of 52 Children Treated for Neuroblastoma Who Developed Dental Abnormalities by Disease Stage and Therapy

INSS stage	No. (%) of patients with dental abnormalities	No. of patients who received radiotherapy (no. with dental abnormalities)
1	3 (75)	0
2	6 (75)	2 (1)
3	1 (25)	0
4	27 (75)	6 (4)

Dental Abnormalities

Dental abnormalities were identified in 37 of the 52 eligible children (71%), who received a total of 113 examinations. Normal panoramic radiographs preceded those showing abnormalities in 6 of the 24 patients for whom multiple panoramic radiographs were available. Microdontia occurred in 20 patients (38%), one of whom had generalized microdontia. Root stunting was present in 9 of our patients (17%), hypodontia in 9 (17%), and enamel hypoplasia in 9 (17%, Table II); 18 patients (35%) had more than one type of abnormality.

In addition, 15 (29%) patients had more than 4 (mean, 7.8) decayed, filled primary teeth either at the beginning of or during treatment. The excessive caries in one patient was attributed to baby bottle tooth decay [25]; only his maxillary incisors were affected. However, the other 14 of these patients had caries in both incisors and molars. Most of the patients with excessive caries had unsatisfactory oral hygiene and a history of excessive carbohydrate intake. Though the caries in primary dentition was increased, the number in permanent teeth was the same as in the normal population.

DISCUSSION

Because of the early age at which children are treated for neuroblastoma (median among our study population, 1.5 years), both the primary and permanent dentition are at risk for treatment-associated abnormal development. We found that 71% of our study group had clinically or radiographically identifiable dental abnormalities. The observed abnormalities comprised absence of and abnormally small permanent teeth, pronounced shortening of primary and permanent tooth roots (Figs. 1–3), and excessive caries, and severe enamel hypoplasia of primary and permanent teeth. Treatment of neuroblastoma commonly includes doxorubicin, cyclophosphamide, carboplatin, cisplatin, and etoposide. In rats, vincristine, vinblastine, and cyclophosphamide delay or disrupt odontogenesis, as manifested by the increased number of incremental lines and deranged production of dentinal matrix after administration of these drugs [26–30]. The

TABLE II. Distribution of Abnormal Teeth in Patients Diagnosed With Neuroblastoma at ≤1 Year vs. Those Diagnosed as >1 Year of Age*

	Microdontia		Root stunting		Hypodontia		Enamel hypoplasia	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
Incisors	9	0	3 (1)[a]	1	1	0	0 (1)	0 (1)
Canines	7	0	1 (1)	1	0	0	1	0
Bicuspids	3	5	0 (1)	1	2	2	0	0
First molars	1	0	2 (1)	1	0	0	1	1
Second molars	0	1	2 (1)	2	0	0	0 (1)	0 (2)
Third molars	0	1	0	0	0	1	0	0

*Patients ≤1 year of age are group I; patients >1 year of age are group II.
[a]Numerals in parenthesis indicate abnormal primary teeth.

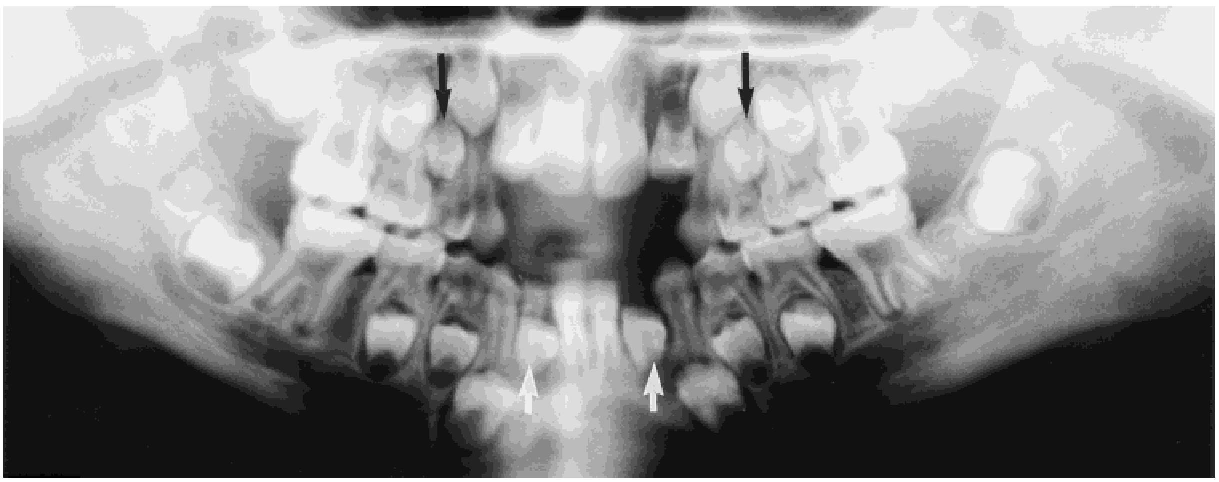

Fig. 1. This panoramic radiograph of an 8-year-old girl diagnosed at age 1.2 years with stage D neuroblastoma shows microdontia of the maxillary first bicuspids (black arrows) and severe root stunting of mandibular permanent lateral incisors (white arrows).

incremental lines seem to result from the effect of these agents on collagen precursors in the osteoblasts and chondrocytes [8,27]. If the alteration or amelogenesis or odontogenesis is severe enough, a whole tooth may fail to develop [8]. Since cyclophosphamide is a putative agent for odontogenesis, children with neuroblastoma are at risk for altered dental development because cyclophosphamide is included in most chemotherapeutic regimens for this disease.

Hypodontia of at least one of the third molars occurs in 35% of the general population [31]; therefore this abnormality may not be treatment-related in our series. However, the frequency of the remaining dental abnormalities found in our study population is excessive. Hypodontia (excluding third molars) ranges from 1.6% to 9.6% in differing world populations [34] but was present in 17% of our patients.

More than a third of our patients developed isolated microdontia, and one patient developed generalized microdontia. Microdontia of third molars or maxillary lateral incisors is frequent in the general population, but microdontia of other teeth occurred in 33% (17 of 52) of the patients we studied. Hypodontia and microdontia can cause abnormal spacing and drifting of teeth, potentially resulting in poor dental alignment, and malocclusion. In addition, hypodontia and root-stunting (which rarely occur in the general population but affected deciduous and permanent dentition of 17% of our patients) may preclude adequate orthodontic anchorage [31,32]. These deficiencies may lead to long-term functional morbidity [1,2,7], thereby placing patients with these dental abnormalities at increased risk for periodontal disease and subsequent tooth loss.

Prior studies have shown that children receiving chemoradiation therapy have an increased risk of dental caries [3,12,21], and this predisposition can persist for many years after therapy [10,21]. Children who receive radiation therapy to the head and neck and those who receive whole body irradiation of 1000 cGy may develop reduced salivary flow [3–5], which can alter the pH of the saliva, change the oral flora, and increase the subsequent risk of excessive dental caries.

Dietary factors and parent permissiveness may also contribute to the increased dental caries in pediatric oncology patients. Frequently these children develop stomatitis and oral mucosal ulcerations. During these periods, they may prefer sweet foods, thereby further promoting tooth decay [6]. In addition, medically

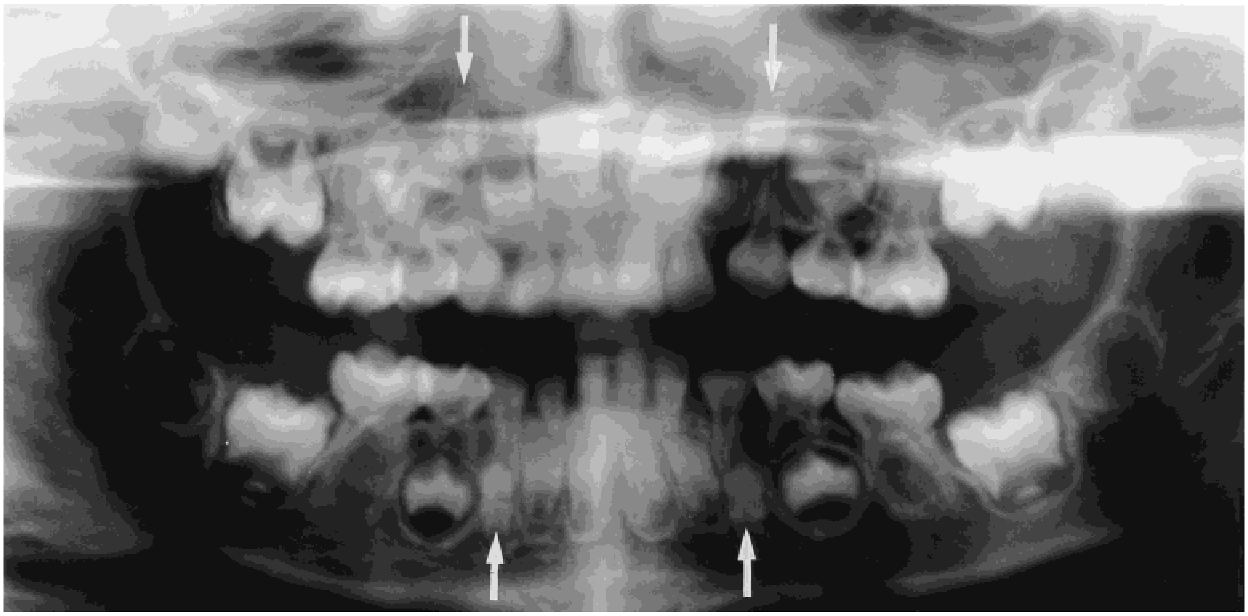

Fig. 2. This panoramic radiograph of a 4 1/2-year-old girl shows severe microdontia of all four developing canines (arrows). Severe root stunting is evidenced in the primary maxillary second molars and incisors, and in the mandibular primary first molars. This child was diagnosed in infancy with stage C neuroblastoma. Clinically, she had concurrent severe enamel hypoplasia of mandibular permanent central teeth.

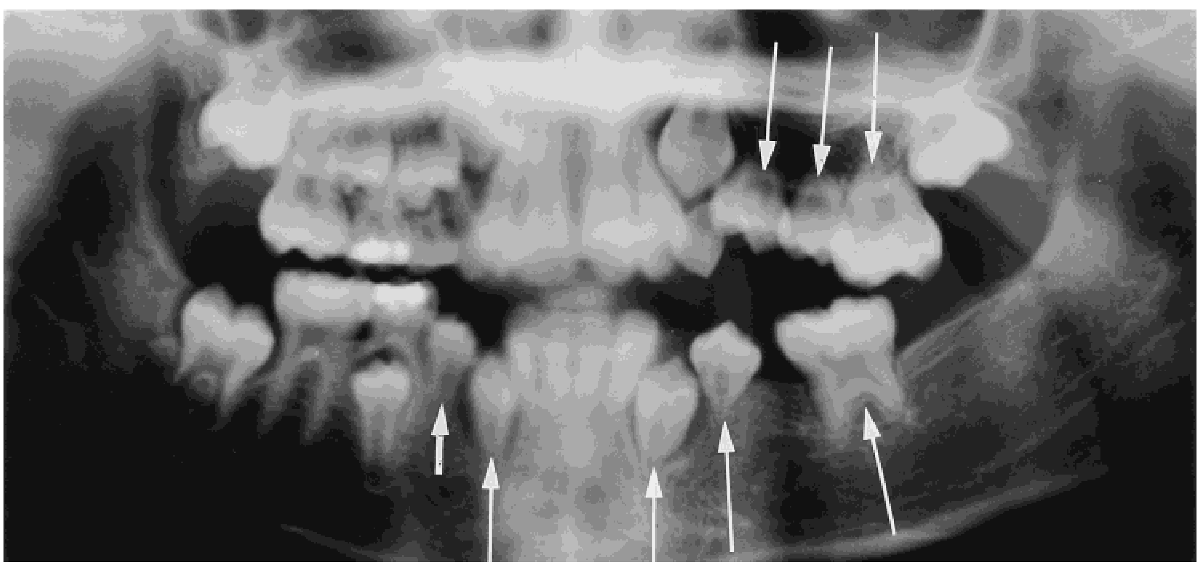

Fig. 3. This 9 1/2-year-old boy was diagnosed at 4.3 years of age with stage D neuroblastoma, requiring left mandibular radiation therapy in addition to systemic chemotherapy. Treatment resulted in severe root stunting of maxillary and mandibular bicuspids and canines and left mandibular and maxillary first molars (long arrows); microdontia of the right mandibular first bicuspid (white arrow); and hypodontia of numerous permanent teeth. The asymmetric severity of abnormal odontogenesis is related to left mandibular irradiation.

compromised patients often require high carbohydrate diets in order to maintain caloric intake [35]. Oral hygiene may be compromised during treatment because children may be prohibited from brushing their teeth during bouts of severe thrombocytopenia and neutropenia [6,21]. Among our study population, oral hygiene may have been further compromised by the patient's age at diagnosis; nearly half of the patients were younger than 1 year when they began treatment. Children this age frequently are not able to brush their own teeth adequately and parents are often unable or unwilling to brush for their children.

The present study demonstrates the importance of meticulous oral hygiene in pediatric oncology patients, especially during treatment. The excessive intake of refined carbohydrates and the accumulation of debris and plaque on the teeth synergize to promote the formation and progression of dental caries. To prevent systemic bactere-

mias from oral flora, health care personnel often tell patients receiving chemotherapy to discontinue tooth brushing during periods of severe thrombocytopenia and neutropenia. However, accumulation of debris on the gingivae can actually induce inflammation and create a focus of infection. Gingival trauma should be minimized during episodes of severe thrombocytopenia or neutropenia, but good oral hygiene needs to be maintained; very soft bristle brushes are available that effectively remove debris without inducing trauma. Parents may also be shown how to use a moistened gauze or facecloth, and the sponge ''toothettes'' for cleaning teeth. If the child is able to swish and hold liquids, the daily use of chlorhexidene gluconate (0.12%) rinses may also be incorporated into the oral care regimen. Parents must be educated on the importance of good oral hygiene during oncotherapy and informed of the detrimental effects of excessive dietary carbohydrates on the teeth.

CONCLUSION

Children treated for neuroblastoma are at increased risk for the development of dental abnormalities including caries, microdontia, root stunting, enamel hypoplasia, and hypodontia. These abnormalities can lead to conditions which may compromise the quality of life of pediatric cancer survivors. Our findings may be extrapolated to children treated for other childhood cancers at an early age. Early, frequent dental examinations and an intense oral hygiene program before, during, and after therapy may improve overall dental health.

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